AMERICAN JOURNAL OF PHYSICAL ANTHROPOLOGY 104:213–226 (1997)

Recognition of Sickle Cell Anemia in Skeletal Remains of Children

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KEY WORDS anemia; bone pathology; children; iron deficiency

ABSTRACT The present study discusses in detail the osteological changes associated with sickle cell anemia in children and their importance in differential diagnosis. Posterior calcaneal and specific articular surface disruptive metacarpal lesions are diagnostic for sickle cell anemia. Calvarial thickening, tibial and femoral cortical bone thickening, and bowing are of more limited utility in differential diagnosis. Granular osteoporosis, pelvic demineralization and rib broadening are nonspecific. Localized calvarial "ballooning," previously not described, may have diagnostic significance. Bone marrow hyperplastic response (porotic hyperostosis) in sickle cell anemia produces minimal radiologic changes contrasted with that observed in thalassemia and blood loss/hemolytic phenomenon.

Two other issues, the osteological criteria for discriminating among the anemias and the purported relationship between porotic hyperostosis and iron deficiency anemia, are also discussed. There is sufficient information to properly diagnose the four major groups of anemias, and further, to establish that iron deficiency is only indirectly associated with porotic hyperostosis. The hyperproliferative bone marrow response (manifest as porotic hyperostosis) to blood loss or hemolysis exhausts iron stores, resulting in secondary iron deficiency. Am J Phys Anthropol 104:213–226, 1997.

A prevalent subject of study in palaeopathology has been structural alterations attributed to anemia. The data are frequently used to gain insight to broad biological processes (e.g., population migration and diffusion of genes, origin of agriculture, and the relationship between economic transition, evolutionary processes, etc.), in addition to defining the health of a specific population (Hooton, 1930; Angel, 1966; El-Najjar et al., 1975; El-Najjar and Robertson, 1976; Lallo et al., 1977; Mensforth et al., 1978; Mensforth, 1985; Walker, 1985, 1986; Palkovich, 1987; Hershkovitz et al., 1991). The validity of this approach is predicated on the ability to distinguish accurately among the varieties of anemia. Although Ortner and Putschar (1981: 263) suggested that "differential diagnosis of anemia in dry skeletal specimens may not be possible without considering other variables, including biochem-

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Received 6 February 1996; accepted 16 July 1997.

istry," there may be reason for greater optimism. Subsequent studies (e.g., Rothschild and Sebes, 1981; Stuart-Macadam, 1987a,b; Resnick and Niwayama, 1988; Johanson, 1990; Rioja et al., 1990; Babhulkar et al., 1995; Bastian, 1995) suggested additional signs, which appear diagnostic for specific varieties of anemia.

The rarity of macroscopic descriptions of the skeletal impact of specific varieties of anemias, based on examination of the entire skeleton of individual(s) with documented case histories, contrasts with the many radiologic reviews (e.g., Britton et al., 1960; Shahidi and Diamond, 1960; Burko et al., 1961, 1963; Lanzkowky, 1968; Stuart-Macadam, 1987a). As the latter often emphasize subtle findings, it seemed appropriate to explore macroscopic correlates of such phenomena. The aim of the present study is to describe in detail the osteologic changes in a child known to have sickle cell anemia (SCA).

MATERIALS AND METHODS

The skeleton (HTH 1784) of a 6-year-old boy with splenomegaly and peripheral and central thrombotic phenomena, secondary to sickle cell anemia (1928 Lakeside Hospital record no. 122388), was examined at the Cleveland Museum of Natural History, where the skeleton is now housed in the Hamann-Todd collection.

The skeleton was complete, with all epiphyses. Macroscopic examination was performed, especially noting changes in calvarial bones, facial architecture and sinuses, long bones and ribs. Autopsy x-rays were compared to those taken of isolated bones. The morphometrical characteristics of HTH-1784 used to assess developmental problems were derived from three sources: 1) measurements taken directly from the bones [clavicle length, scapula height and breadth, three measurements on each rib, innominate height and width, size of vertebral canal, size of basivertebral foraminae and cranial module (maximum length + maximum breadth + basion-bregma height/3) following methods described in Bass (1987), 2) metrical information recorded by Todd from the cadaver (e.g., head measurements), and 3) metrical information from the hospital records (stature and weight). Comparative growth data were obtained from Herskovits (1924), Simmons and Todd (1938), and Simmons (1944).

Our general control group (aged 4 to 16) comprised of 24 skeletons of children and subadults from the Hamann-Todd Osteological Collection (HTOC) and 26 children from the collection of the Department of Anatomy and Anthropology, Tel Aviv University (TAUOC). As only five children, aged 6, of the control sample (two from the HTOC and three from the TAUOC) were available, to test the correspondence of the HTH-1784 child measurements to his age cohort, linear regression analysis was performed. Linear regression along with the 95% confidence interval was computed using measurements taken from all available children within the 4 to 9 year age interval. To avoid deviation of linearity, no measurements from older children were included. Each measurement of the HTH-1784 child was then compared against the respective predicted mean at each age.

A special macroscopic examination of calcanei from all subadults (47) and 200 adults from the Hamann-Todd collection was also performed.

RESULTS

Skeletal alterations were predominantly those reflecting bone marrow hyperplasia and vascular compromise (e.g., thrombosis). The major changes observed in the skeleton are described below, from a regional perspective.

The skull

General thickening of the calvarium was present (Fig. 1). A marked ectocranial surface disruption (porotic hyperostosis), involving large areas on both sides of the sagittal suture, was limited to the parietal bones (Fig. 2). The thickening of the diploic space was limited (on anteroposterior and lateral x-ray views) to frontal and parietal bones, sparing the coronal suture region, but with mild thickening of the orbital roof. Endosteal resorption of the external diploic plate in the parietal region was so extensive that it resulted in its virtual effacement, with the exception of a multilaminated "ballooned" area in the parietal bone (described below). Slight perpendicular trabeculae were noted

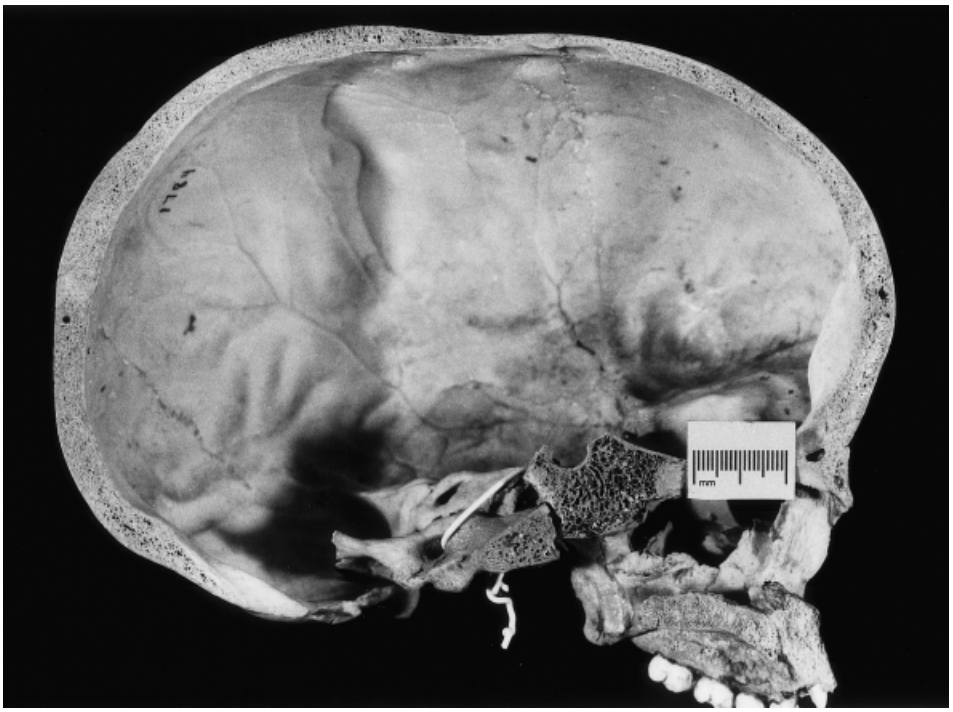

Fig. 1. Midsagittal section of the skull. Thickened frontal, parietal and occipital bone diploic space, with lamellar radiations ("hair-on-end" phenomena) noted only in superior aspect of parietal bone.

in this area, probably representing an early "hair-on-end" reaction. The inner table showed no signs of porosity on macroscopic examination, or thinning on radiologic examination, although a generalized granular texture was noted. The skull size (cranial module) was within the range (95% confidence limits) of the regression of the control group age mean, and shape abnormality was limited to those in the diploic plate, as noted above. Todd's records on the cadaver (maximum head length = 194 mm; maximum head width = 138 mm; auricular height = 117.5 mm) also imply that head size is within the normal range.

Marked ectocranial "ballooning" (as distinct from "bossing," see Discussion) was present in the parietal, frontal and temporal bones. While ectocranial texture was unaffected in those regions, macroscopic examination revealed hyperpigmented (blue-black) punctuate ectocranial discolorations from 0.1 to 0.4 mm in size. Present at a density of 20–40 per cm^2, these "spots" were limited in distribution to the regions of marked ectocranial ballooning. Transillumination of the "ballooned" areas revealed increased density similar to that noted in areas of porotic hyperostosis.

Facial architectural relationships were normal. No pathological changes were observed in the maxillary or frontal sinuses. The hard palate was thickened with accentuation of vertical trabeculae. The lingual aspect of the maxillary alveolar arch was thickened (3–4 mm), producing a medial "swelling" adjacent to the molar teeth. The mandible was robust, with very slight supralingula periosteal new bone deposition.

Shoulder girdle

The size and shape of clavicles (length = 97.9 mm) and scapulae (height = 89.9 mm; breadth = 67.2 mm) were within the 95% confidence limits of the regression of the control group mean age. Slight porosity was present in the metaphyseal regions of clavicles and vertebral region of scapulae. A

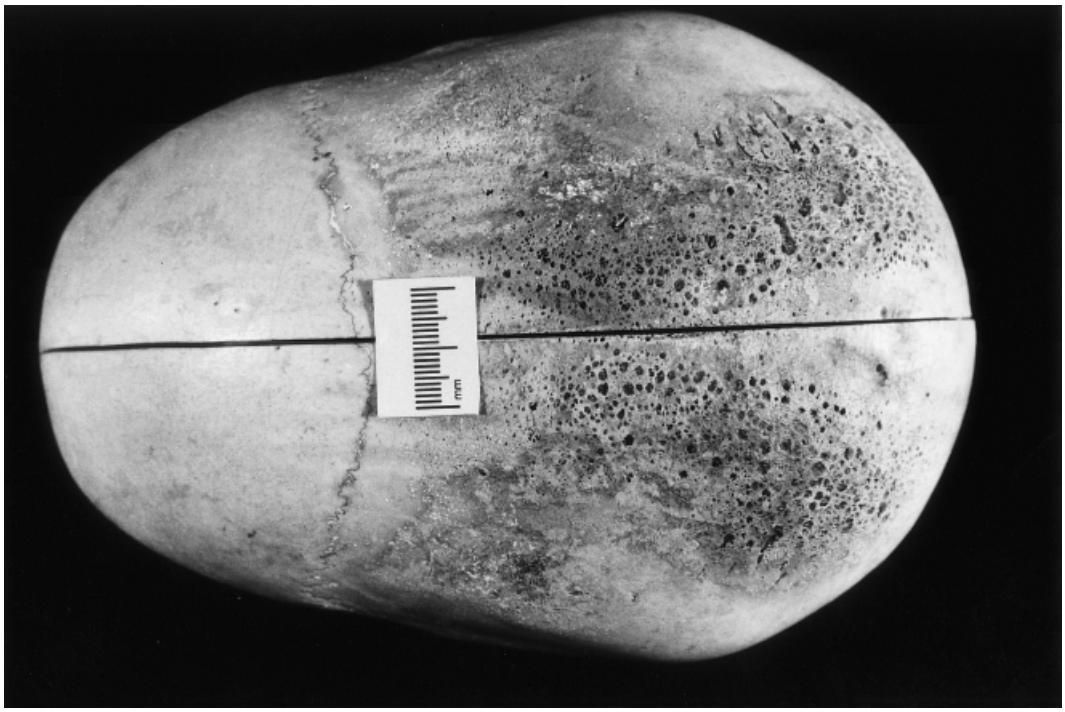

Fig. 2. Superior view of skull. Parietal bone porotic hyperostosis.

minimal amount of new periosteal bone was noted along a 1 cm swath, distributed on the ventral aspect of the entire vertebral margin of the scapulae.

Upper limb

All epiphyses and articular surfaces were free of pathological processes on macroscopic examination. Porosity was noted in the proximal humeral metaphyses, both radial metaphyses (distal significantly more affected than proximal), and the distal ulnar metaphyses. Slight bone deposition was noted in areas of tendon attachment, along the radial and ulnar diaphyses (ulnae more affected than radii). Intracortical bone resorption and mild endosteal scalloping were noted on x-ray examination.

Macroscopic examination of hand and wrist bones was unremarkable, with the exception of cortical disruption of the distal articular aspect of the left second metacarpal. A slight peg-like appearance of the distal epiphyses of the proximal and middle phalanges was noted. Metacarpal lesions included a marginal erosion and a subchondral defect. The latter appeared as a 0.5 mm segment of ordinary cortical bone, surrounded by an undermining lytic zone approximately 2 mm in diameter and 1 mm deep. Endosteal and intracortical bone resorption with minimal linear periosteal new bone formation were noted on the radiographs.

Thoracic cage and vertebrae

The ribs of HTH-1784, compared to the control group, were thicker (third rib: A-P (mid-shaft) = 4.5 mm, Circum. = 23.8 mm; fourth rib: A-P = 5.1 mm, Circum. = 24.2 mm) throughout their entire length (third rib control: $\overline{X}_{A\text{-}P} = 4.20$; $S.D._{A\text{-}P} = 0.67$; $\overline{X}_{circum} = 121.74$; $S.D._{circum} = 2.76$). Endosteal scalloping and intracortical bone resorption, with slight trabecular coarsening, were noted on the radiographs. All vertebrae were of standard size and shape. Vascular foramina (especially the basivertebral) were large, 5 × 4 mm (Fig. 3). A slight porosity was present on the ventral surfaces of lum-

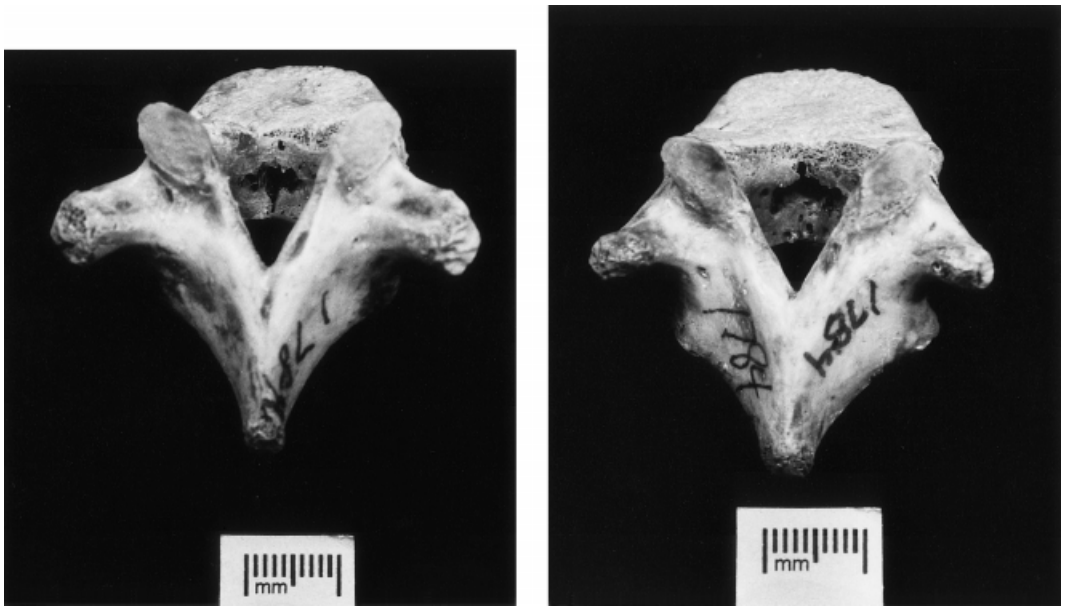

Fig. 3. Postero-superior view of thoracic vertebrae. Enlarged basivertebral foraminae.

bar vertebral bodies. A lateral x-ray of the vertebrae revealed osteopenia with a coarsened appearance of the residual body trabeculae.

Pelvis

The two innominates were high (129.0 mm) and narrow (80.0 mm), with the ilium lacking the typical "mushroom" shape. While the area (product of length and width) of the alae was not increased over that of the control group, the alae were 20% thicker than normal. A large cortical defect was present in each iliac acetabular (articular) surface, penetrated by large vascular foraminae. The pubic and ischial bones were unaffected.

Lower limb

Minimal periosteal reaction was noted on both femoral diaphyses. Metaphyses, epiphyses and articular surfaces were free of any sign of pathological process or developmental disturbances. Two enlarged diaphyseal nutrient foraminae were present in each of the femora. Tibiae and femora were slightly bowed and flattened at midshaft (Fig. 4). Cortical thickening was observed radiologically on the anterior aspect.

Macroscopic foot/ankle abnormalities were limited to the calcanei. Disruption in surface integrity was noted at the superoposterior aspect (Fig. 5), posterior to the area of attachment of the joint (talocalcaneal) capsule. This region of compromised surface integrity was located anterior to the area of attachment of the Achilles tendon and associated bursae. Eleven smooth-walled surface perforations, of irregular size, were located anterior to a 1.5 mm deep, 2 mm $\times$ 3 mm, cresent-shaped depression. A 1 mm $\times$ 2 mm fragment of cortical bone was present at the base of that depression, with its margins partially undermined. The surrounding region had been smoothly excavated. Underlying the 0.5 to 0.7 mm smooth-walled perforations was a cystic area, approximately 3 mm (diameter), with smooth margins. A "dot-dash" pattern of surface discontinuity was noted on the superoposterior surface of the calcaneus, between the insertion area of the talocalcaneal joint capsule and the anterior Achilles bursa.

One or more nutrient foramina(e) were present on 90% of superoposterior calcaneal surfaces in 200 adults. Three out of 47 subadults had multiple small foraminae at

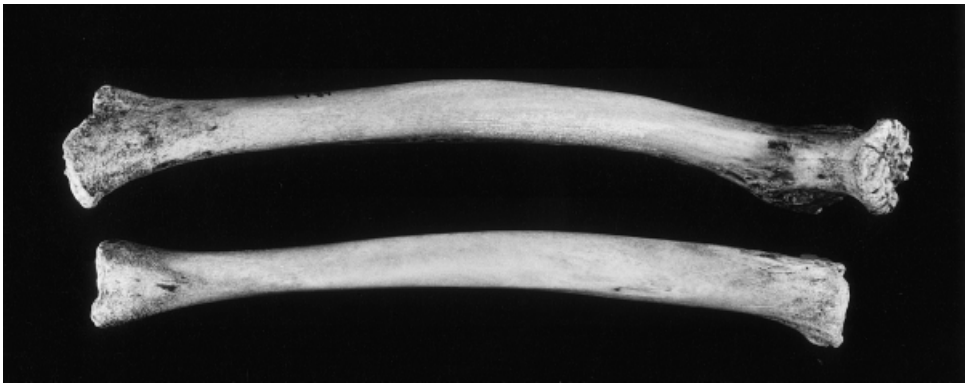

Fig. 4. Medial view of right femur and tibia. Bowed femur and tibia.

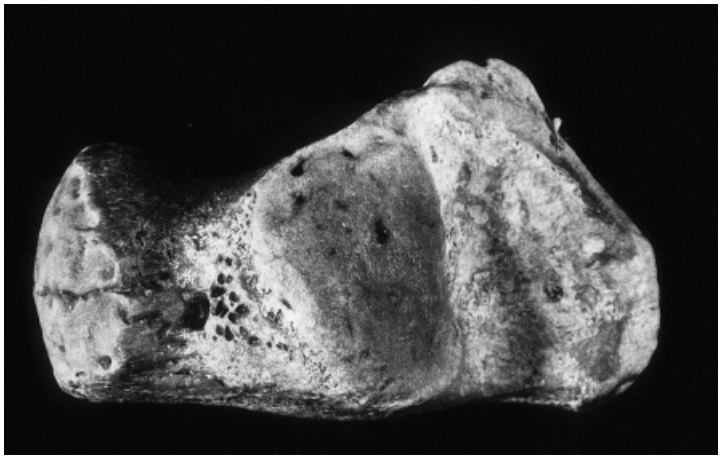

Fig. 5. Superior view of left calcaneus. Surface disruptions in region between the insertion of the Achilles tendon and articular surface (for the talus). Multiple foramena are present on the calcaneal surface, anterior to a large disrupted area. The latter contains what appears to be normal surface bone at the base of the hole.

this location, while the remainder had no surface alterations (other than those attributed to deteriorating processes within the storage drawers). The very thin nature of calcaneal surface bone occasionally allows deteriorating processes within the drawers or post-depositional deteriorating processes in archaeological material. The latter was distinguished from changes of necrosis on basis of broken, unremodelled trabeculae.

Developmental assessment

No discrepancy was found between biological and chronological age. The biological age of HTH-1784, assessed from the teeth and bones (Ubelaker, 1987, 1989; Demirjian, 1980), was 6 to 6.5 years, similar to his chronological age (6 years). The comparison of of the stature (1,212 mm) and weight (29.5 kg) (hospital and Todd records) of HTH-1784 with that of children his age (data collected at the beginning of the century) showed no evidence of developmental delays. The mean stature of children 6 years old, at the beginning of the 20th century, varied (among studies) from 1,157 mm (S.D. 52.0 mm) to 1,177 mm (S.D. 42.8 mm) (Herksovits, 1924; Simmons and Todd, 1938; Simmons, 1944). Our observations on the epiphyses (as described above) confirmed that HTH-1784 had no developmental disturbances.

DISCUSSION

The birth of this child, 12 years after the first clinical report of sickle cell anemia (Herrick, 1910), fortuitously allowed identification of the etiology of his splenomegaly. This fulfilled the a priori requirement in

clinical diagnosis that a phenomenon must be recognized and be codified as distinct. While molecular analysis (to distinguish between the SS and SC varieties of sickle cell anemia) was first reported (Graham, 1924) during the latter portion of his short life, it was unavailable clinically during his lifetime. Given the similarities between the osseous impact of SS and SC disease (Rothschild and Sebes, 1981; Resnick and Niwayama, 1988), absence of that information is of limited importance. It is possible that the polymerase chain reaction amplification of DNA extracted from the skeleton could potentially resolve the type of sickling disease that was present, should its pertinence be demonstrated.

A major problem of a study trying to establish diagnostic criteria, based on the skeleton alone, is whether all atypical bony responses observed are a result of the disease under investigation (in this case SCA). In the following discussion we try to match our osseous findings with data (mainly radiological) obtained from reported cases of sickle cell anemia. We omitted from our final list of diagnostic criteria bony lesions for which a correlation could not be identified, although such correlations remain a possibility.

Recognition of SCA in the skeleton should be carried out in two successive stages: the first, to identify the case as a pathology associated with the hematopoietic system (use Table 1); the second, to try to identify the disease itself (use Table 2).

Through the present case we demonstrate the approach above. The first question is: Do we have sufficient osteologic evidence to conclude that HTH-1784 had a problem associated with the hematopoietic system? What are other possible explanations for the observed pathological changes?

General differential diagnosis

Although diseases of the hematopoietic system are known to affect the bones in a very characteristic manner (Table 1), few are actually exhibited. Further, the "classic" characteristics are rarely present in young individuals (aged <9 years).

The best indications for hematopoietic diseases are to be found in the skull (Tables 1 and 2). The most prominent osteologic changes in the skull of HTH-1784 were parietal osteoporosis, parietal, frontal and temporal bone "ballooning," and parietal and frontal diploic space thickening. While porotic hyperostosis was clearly present (Fig. 2), the "hair-on-end" radiologic appearance was subtle and difficult to recognize. This is in accordance with clinical recognition of its rarity and limited severity (2–8%) in sickle cell anemia (Carroll and Evans, 1949; Ehrenpreis and Schwinger, 1952; Sebes and Diggs, 1979).

Cranial "ballooning" (swelling) is different from cranial "bossing." The latter is a normal phenomenon which occurs in both children and adults. Lateral dome-shaped protrusion of the temporal regions and regions around the anterior part of the superior temporal lines are commonly seen in children. However, they are usually not associated with changes in the texture of the ectocranial plate, or with an increase in diploic space.

Axial manifestations in HTH-1784 included slightly enlarged ribs, hypervascularization of vertebrae and innominate (alae) thickening. Absence of vertebral endplate indentation is not surprising, given the subject's age. Vertebral changes (Fig. 6) are seen in less than 10% of individuals with sickle cell anemia (Reynolds, 1966; Kaklamanis, 1984; Johanson, 1990), their occurrence limited to those who have reached the age of 8 years (Karayalcin et al., 1976). Gradual indentation of adjacent vertebral end plates may produce a "fish-mouth" appearance on lateral x-ray (Fig. 6). Discontinuous indentation can produce an "H"-shaped vertebral appearance (Reynolds, 1966; Cassady et al., 1967; Kaklamanis, 1984; Resnik and Niwayama, 1988).

Appendicular skeletal changes predominantly affected the lower extremities. The femora and tibiae manifested slight bowing and cortical bone thickening, but no obvious narrowing of the medullary cavity. Cortical disruption was noted on the superior border of the calcanei, between the site of Achilles tendon insertion and the talar articular surface.

Considering the nature of the osteologic changes in HTH-1784, it is no wonder that the diagnosis of anemia in skeletons of past

TABLE 1. Osteological changes associated with diseases of the hematopoietic system, by bones

Characteristics	Thalassemia	Sickle cell	Secondary iron deficiency	Primary iron deficiency
Skull				
Calvaria	+	12–62%[4]	+	+
Granular osteoporosis	+	1–8%	+	+
Focal pseudo-radiolucent areas[6,7]	–	R	–	–
Calvarial thickening	+	+	+	+
Thinning of outer and inner table	+	25%	+	+
Widening of diploe space	+	+	+	+
Porotic hyperostosis	+	+	+	+
"Hair-on-end" (porcupine quill) appear. (x-ray)	+	R	R[5]	R
Diffuse calcification (chalky appearance)[6]	–	+	–	–
Face				
Large head	+	–	–	–
Lateral displacement of orbits	+	–	–	–
Sunken nasal bridge	+	–	–	–
High, prominant cheek bone ("rodent facies")	+	–	–	–
Maxillary swelling	+	–	–	–
Enlarged upper alveolar ridge	+	–	–	–
Mandible (alveolar bone)				
Increased radiolucency	–	+	–	–
Coarsened trabeculae[1]	–	+	–	–
Sternum				
Sternal widening	+	R	–	–
Sternal cupping[3]	–	8%	–	–
Pelvis				
Demineralization	+	32%	R	R
Protrusio acetabuli	+	20%	–	–
Patchy sclerosis	–	24%	–	–
Coarse trabeculation	+	5%	R	R
Medullary hyperplasia	+	+	–	–
Avascular necrosis	–	1%	–	–
Vertebrae				
Osteoporosis	+	+	R	+
"Codfish vertebra"	R	10%	–	–
Squared off end plate depression (H-vertebrae)	R	+	–	–
Enlarged basivertebral foraminae.	–	+	–	–
Collapse (compression fractures)	R	+	–	–
Shape changes: increased width reduced height	R	+	–	–
Sclerosis (dense bands)	–	+	–	–
Tubular bones				
Demineralization	+	62%	R	R
Thinned cortex	+	+	R	R
Widening medullary space	+	+	R	R
Microfractures	+	–	–	–
Pathologic fractures	+	R	–	–
Widening of metaphyses and epiphyses	+	–	–	–
Retarded bone age	–	+	–	–
Delay closure of growth plate	–	+	–	–
Premature partial epiphyseal plate closure	+	–	–	–
Growth deformity	+	–	–	–
prox. humeral epiphyses[2]	+	+	–	–
prox. femoral epiphyses[2]	–	+	–	–
distal femoral epiphyses[2]	+	–	–	–
distal tibial slant[2]	+	39%	–	–
Bone infarcts	–	+	–	–
Bone-within-bone appearance (osteonecrosis)	–	+	–	–
Enlargement of nutrient foramina	+	+	–	–
Coarse trabeculation	+	15%	R	R
Patchy sclerosis	+	27%	–	–
Osteomyelitis	–	+	–	–
Lace-like appearance of external surface	+	–	–	–
Elongation (pseudo-Marfan's syndrome)	–	+	–	–
Ribs				
Broadening of posterior aspect	+	32%	R	R
Demineralization	(+)	26%	R	R
Coarse trabeculation	+	4%	R	R
Sclerosis	+	32%	–	–
Linear density ("rib-within-rib")	+	–	–	–
Cortical erosions (and thinning)	+	–	–	–
Dentition				
Disorderly teeth eruption	+	–	–	–
Malocclusion of jaws (maxillery overbite)	+	–	–	–
Structural abnormality of the teeth	–	+	–	–

The data presented in Table 1 are derived from numerous publications; for references, see Table 2.
[1] Surrounded by osteoporosis with coarse trabeculae, produces a "step-ladder appearance" is occasionally revealed on x-ray.
[2] After the age of 10 years.
[3] Childhood phenomena.
[4] Number expresses relative population frequency.
[5] R = rare (manifest in less than 1%).
[6] Only in individuals >50 years.
[7] Radiolucent areas correspond to hyperplastic bone marrow surrounded by dense sclerotic bone (not lytic areas).

TABLE 2. Osteological changes associated with diseases of the hematopoietic system[1]

Characteristics	Thalassemia	Sickle cell	Secondary iron deficiency[2]	Primary iron deficiency[3]
Osteopenia				
Generalized osteoporosis	+	+	+	+
Central vertebral endplate depression	−	+	−	−
Localized osteolysis	−	+	−	−
Mottled osteolysis	−	+	−	−
Growth disturbance				
Epiphyseal shortening	−	+	−	−
Epiphyseal closure delay	−	+	−	−
Tibiotalar deformity	−	+	−	−
Avascular necrosis				
Collapse of articular surface	−	+	−	−
Cortical discontinuity	−	+	−	−
Widened, flattened epiphysis	+	+	−	−
Epiphysio-metaphyseal overlap	+	+	−	−
Femoral head collapse/mushroom shape	−	+	−	−
Proximal humeral collapse	−	+	−	−
Microinfarcts				
Central metaphyseal plate depression	−	+	−	−
Triangular epiphyseal deformity[4]	−	+	−	−
Juxta-articular	−	10%	−	−
Calcaneal surface lesion	−	9%	−	−
Sclerosis	−	+	−	−
Medullary canal infarct	−	+	−	−
Hand foot syndrome[5]	+	17%	−	−
Lytic areas in tubular bones	+	+	−	−
Thinned cortices	+	+	−	−
Shortening of digits	−	+	−	−
Subperiosteal new bone formation	−	+	−	−
Patchy radiolucency/moth-eaten appearance	+	+	−	−
Focal osteosclerosis	+	+	−	−
Osteomyelitis	−	+	−	−

[1] Derived from Cooley and Lee, 1926; Cooley et al., 1927; Moseley, 1929a,b; Moore, 1929; Diggs et al., 1937; Caffey 1937, 1952; Carroll and Evans, 1949; Ehrenpreis and Schwinger, 1952; Prowler and Smith, 1955; Carroll, 1957; Trowell et al., 1957; Eng, 1958; Sherman, 1959; Barton and Cockshott, 1962; Burko et al., 1961, 1963; Robinson and Rodnan, 1965; Sarnat, 1962; Moseley, 1963, 1974; Watson et al., 1963; Hewett and Van Nice, 1964; Currarino and Erlandson, 1964; Argen and Sullivan, 1966; Soni, 1966; Aksoy et al., 1966; Reynolds, 1966; Reynolds, 1983; Diggs, 1967; Cassady et al., 1967; Lanzkowsky, 1968; Lagundoye, 1970; Patel, 1973; Mourshed and Tuckson, 1974; Kanyerezi et al., 1974; Espinoza et al., 1974; Palmer, 1975; Shaub et al., 1975; Karaylcin et al., 1976; Keitel et al., 1976; Worrall and Butera, 1976; Leichtman et al., 1978; Gratwick et al., 1978; Sebes and Diggs, 1979; Rothschild and Sebes, 1981; Dorwart and Schumacher, 1981; Levine et al., 1982; Lee et al., 1981; Baker and Demos, 1982; Zimmerman and Kelley, 1982; Dardel and Gerster, 1983; Gorriz et al., 1983; Lawson et al., 1981, 1984; Exarchou et al., 1984; Kaklamanis, 1984; deCeulaer et al., 1984; Fink et al., 1984; Keller, 1982; Redman and Nelson, 1985; Scutellari et al., 1985; Stuart-Macadam, 1987a; Hanker and Amstutz, 1988; Resnick and Niwayama, 1988; Orzincolo et al., 1989; Hernigou et al., 1989, 1991; Korovessis et al., 1990; Johanson, 1990; Arman et al., 1992.
[2] E.g., hemolytic anemia or blood loss induced marrow hyperplasia.
[3] Hypoplastic bone marrow.
[4] "Peg-in-a-hole" deformity, noted only in older children and adults.
[5] Known also as "sickle cell dactylitis," a phenomenon noted in children aged 6 months to 2 years. It is very rare after 6 years of age, representing disappearance of red marrow from the small bones of the hands by this age.

populations is so difficult. Granular osteoporosis, pelvic demineralization and rib broadening are quite nonspecific. Calvarial thickening and tibial and femoral cortical bone thickening and bowing are more limited in differential diagnosis. Osteomalacia, Paget's disease, and acromegaly can also produce this pattern. Localized calvarial "ballooning" is of unknown differential significance at this time. Differential diagnosis should include leukemia, osteomyelitis, treponematoses, hemophilia, juvenile rheumatoid arthritis (JRA), skeletal dysplasia (e.g., trichorhinophalangeal syndrome), rickets, thalassemia and other disorders resulting in hemolysis (e.g., glucose-6-phosphate dehydrogenase deficiency), and secondary iron deficiency anemia (see next section). Osteomyelitis, which often occurs in individuals with sickle cell anemia (Burko et al., 1963; Lagundoye, 1970), is easily recognized because of the associated distortion of bony architecture (Resnick and Niwayama, 1988; Rothschild and Martin, 1993). The limited periosteal reaction and its distribution in HTH-1784 contrasts with more extensive involvement in treponemal disease (Ortner and Putshar, 1981; Resnick and Niwayama, 1988; Roths-

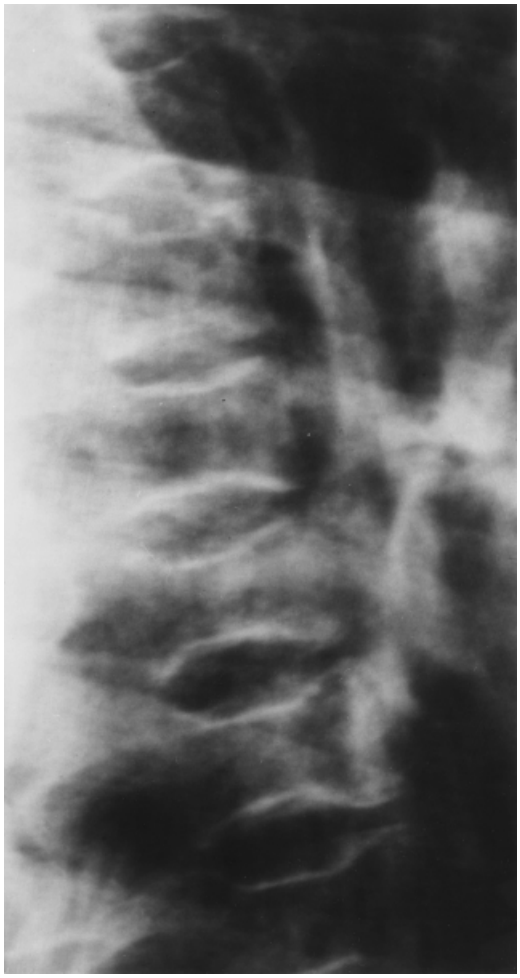

Fig. 6. Lateral x-ray view of thoracic vertebrae. Growth plate indentation patterns produce fish-mouth appearance of disc space (central portion of figure) and H-shaped appearance of vertebrae (superior and inferior aspects of figure).

child and Rothschild, 1995), even if the "sabre-shin" reaction was not considered in differential diagnosis. Although fungal disease (e.g., histoplasmosis) can cause digital periosteal reaction (Resnick and Niwayama, 1988), pelvic demineralization, rib broadening, calvarial thickening and ballooning, tibial and femoral cortical bone thickening and bowing, posterior calcaneal and articular surface metacarpal lesions do not occur (Hewett and van Nice, 1964; Diggs, 1967; Lagundoye, 1970; Karayalcin et al., 1976; Leichtman et al., 1978; Rothschild and Sebes, 1981). Similarly, the various fibrous dysplasia produce characteristic, well-defined changes in skeletal morphology and internal structure (Resnick and Niwayama, 1988), quite different from the demineralization, rib broadening, calvarial thickening, tibial and femoral bowing, posterior calcaneal and articular surface metacarpal lesions seen in HTH-1784 (Diggs et al., 1937; Hewett and van Nice, 1964; Lagundoye, 1970; Karayalcin et al., 1976; Leichtman et al., 1978; Rothschild and Sebes, 1981). Rickets is relatively easy to distinguish from sickle cell anemia. Epiphyseal and metaphyseal "cupping, widening and fraying," ricketic rosary, and pseudofractures (on x-ray) (Resnick and Niwayama, 1988) characteristic of rickets were not seen in HTH-1784, while generalized rib broadening and posterior calcaneal erosive disease are not seen in rickets.

Major erosive disease, axial (e.g., zygapophyseal or sacroiliac) joint erosions, fusion of axial (cervical zygapophyseal) and/or peripheral joints, and micrognathia are all signs of juvenile rheumatoid arthritis, and are not found in HTH-1784 (Resnick and Niwayama, 1988; Buikstra et al., 1990). Premature epiphyseal closure and/or ballooned epiphyses occur in juvenile rheumatoid arthritis, tuberculosis and hemophilia (Resnick and Niwayama, 1988; Rothschild and Martin, 1993). While subchondral erosions may occur in hemophilia, absence of epiphyseal overgrowth and intraosseous cysts (pseudotumors) in HTH-1784, eliminate this diagnostic consideration.

Differential diagnosis among the hematopoietic diseases

Even if all the requirements needed to diagnose (in an archaeological skeleton) a disease of the hematopoietic system are met (Table 1), the challenge of identifying the actual disease still exists.

Comparing our observations on HTH-1784 to known osteologic changes associated with disease of the hematopoietic system (Table 2) exemplifies the challenge of specific diagnosis. Much of the diagnostic "list" (e.g., growth disturbance, microinfracts, hand-foot syndrome, etc.) was not demonstrated in HTH-1784. Observation of such changes in a single individual with SCA

under age 9 is infrequent in clinical populations. However, those present may be of great validity (see Table 2) in differentiating SCA from other hematopoietic diseases.

Of the osteologic changes manifested by HTH-1784, only the posterior calcaneal and articular surface metacarpal lesions appear diagnostic for sickle cell anemia (Diggs et al., 1937; Hewett and van Nice, 1964; Lagundoye, 1970; Karayalcin et al., 1976; Leichtman et al., 1978; Rothschild and Sebes, 1981). As specific alterations are noted in only 14% of individuals with sickle cell anemia (Rothschild and Sebes, 1981), an overall picture must be utilized in differential diagnosis [unless individual findings are pathognomonic (e.g., calcaneal lesions are present)]. The calcaneal lesions noted in sickle cell anemia are quite distinct from the broken, unremodelled trabeculae of storage or post-depositional processes and foraminae occasionally noted in otherwise apparently healthy subadults.

Thalassemia classically produces such aggressive marrow hyperplasia, that the "hair-on-end" phenomenon is relatively common. This is in contrast to its rarity in sickle cell anemia (Carroll and Evans, 1949; Ehrenpreis and Schwinger, 1952; Diggs, 1967; Sebes and Diggs, 1979). As facial bone involvement is seen only in thalassemia (Resnick and Niwayama, 1988), it is an important diagnostic finding when present. "Hand-foot-syndrome," which occurs in 17% of individuals with sickle cell anemia, is not diagnostic, as it also occurs in thalassemia, fungal infections, rickets, leukemia and perhaps juvenile rheumatoid arthritis (Burko et al., 1963).

Permeative cortical lesions and radiolucent metaphyseal bands (on x-ray), so characteristic of leukemia (Resnick and Niwayama, 1988), were not seen in HTH-1784.

Infarction of long tubular bones and calcanei appear only in sickle cell anemia and allow confident diagnosis when present. The limited occurrence of this phenomena requires analysis of the overall nature and pattern of osseous changes (Tables 1 and 2), if confident diagnosis is to be obtained. The diagnostic significance of the reported findings are indicative of sickle cell anemia, and not a sickle cell trait. The latter is not known to produce bony changes (Resnick and Niwayama, 1988).

Tables 1 and 2 summarize the osteologic changes associated with iron deficiency (primary and secondary). Iron deficiency anemia must be considered separately, as the osseous changes appear related to the primary disease (bone marrow hyperplasia secondary to hemolytic anemia, ineffective erythropoiesis, or response to blood loss) (Fairbanks and Beutler, 1995), rather than to the iron deficiency. Disorders stressing hematologic homeostasis (e.g., hemolytic anemia, ineffective erythropoiesis, blood loss secondary to parasitic infections) result in a hyperplastic marrow response. The latter typically progresses until essential nutrients/cofactors are consumed.

Any relationship between iron deficiency and porotic hyperostosis teleologically must be indirect. After all, the very presence of the "hair-on-end" phenomenon and porotic hyperostosis identifies hyperplastic bone marrow. The diagnosis of iron deficiency anemia implies that there is inadequate iron for blood cell production (Fairbanks and Beutler, 1995). Thus, iron deficiency produces hyporegenerative marrow (Fairbanks and Beutler, 1995), the opposite of porotic hyperostosis. Finch (1970:412) had clearly demonstrated the effect of "limited iron supply . . . in limiting marrow proliferation." Although iron deficiency cannot produce porotic hyperostosis, the conditions that produce porotic hyperostosis can induce iron deficiency anemia. Any process that increases marrow activity increases consumption of basic nutrients (Fairbanks and Beutler, 1995). Iron stores are typically the most rapidly depleted, resulting in iron deficiency and secondary iron deficiency anemia. Several successive stages of iron deficiency are recognized: Initially decrement in storage iron occurs, without decline in level of functional iron compounds (iron depletion). After iron stores are exhausted, lack of iron limits production of hemoglobin and other active compounds that require iron as a constituent or cofactor, and iron-deficient anemia develops (Fairbanks and Beutler, 1995).

Clearly, HTH-1784 did not exhibit any of the bony changes associated with primary or secondary iron deficiency diseases (Tables 1

and 2), which leave us with the SCA option as the most likely diagnosis.

In the present study we discuss in detail the osteologic changes associated with sickle cell anemia in children and the way they can be used in differential diagnosis. Our results show that posterior calcaneal and specific articular surface disruptive metacarpal lesions are the most diagnostic for sickle cell anemia. Traditional diagnostic features (commonly used by anthropologists for SCA), such as calvarial thickening, tibial and femoral cortical bone thickening, and bowing are probably of more limited use in differential diagnosis. Phenomena such as granular osteoporosis, pelvic demineralization, and rib broadening are quite nonspecific. Localized calvarial "ballooning," not previously described, may have diagnostic significance as well. Bone marrow hyperplastic response (porotic hyperostosis) in sickle cell anemia produces minimal radiologic changes contrasted with that observed in thalassemia and blood loss/hemolytic phenomenon.

In the present study efforts have also been made to establish osteologic criteria for discriminating among the four major groups of anemias, based on the literature.

The importance of presenting a single case of SCA derived from the fact that bone lesions attributed to one anemia or another are reasonably common in prehistoric and early historic skeletons. With this paper, we add to the relatively sparse literature on the macroscopically visible bony changes associated with a documented case of sickle cell anemia. Finally, there is no doubt in our mind that one of the challenges to paleopathology mirrors that of forensic investigation—the desire for a clear unbroken "thread" of evidence. Such opportunities are rare, and therefore each such case deserves in-depth analysis. HTH-1784 validates perspectives based on the archeological record and provides an opportunity for future diagnostic verification.

ACKNOWLEDGMENTS

This research was carried out during the sabbatical of one of the authors (I.H) at the Cleveland Museum of Natural History. It is part of collaborative research project entitle "Dynamic Pattern in Human Skeletal Biology" between the Laboratoire d'Anthropologie Biologique, Faculté de Médecine de Marseille, Université de la Méditerranée, France; Department of Physical Anthropology, Cleveland Museum of Natural History and Department of Anatomy, Case Western University, Cleveland, Ohio, USA; Arthritis Center of Northeast Ohio, Youngstown, Ohio and Department of Anatomy and Anthropology, Sackler Faculty of Medicine, Tel Aviv University, Israel.

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